b.) Remarks

Claims 3 and 16 have been amended in order to recite the present invention with the specificity required by statute. Additionally, claims 4-5, 8-12, 19-20 and 22-25 are amended for better dependency and/or idiomatic usage, and new claims 26-39 are presented in order to more specifically recite various preferred embodiments of the present invention. The subject matter of the amendment is found in the specification as filed, *inter alia*, at page 4, line 6, page 5, line 26 and page 12, lines 14-15. Accordingly, no new matter has been added.

Claims 1-6, 8 and 12-20 are rejected under 35 U.S.C. §102 as anticipated by Law (U.S. Patent No. 4,933,121).

The Examiner states Law discloses liposomal compositions containing macromolecules such as proteins and enzymes. The liposomes are oligolamellar, e.g., have more than two bilayers. The transition temperature of the phospholipids used is about 42 degrees and the sizes of the liposomes are 600 nm. According to the Examiner, it would have been obvious to prepare smaller liposomes as necessary.

In contrast, the present provides liposomes having an average particle size of 120-500 nm. This feature, at least, is not taught by the prior art.

Claims 1-7, 10, 12-17, 19-21, 23 and 25 are rejected as anticipated by Woodle (U.S. Patent No. 5,356,633). As relied upon by the Examiner, Woodle is said to disclose 160nm multilamellar vesicles that contain steroidal and non-steroidal anti-inflammatory agents and methotrexate. The vesicles are prepared using PEG-DSPE, DPPC, DSPC and cholesterol.

However, Woodle's liposomes contain cholesterol; Woodle does not teach a liposome prepared of lipids consisting of phospholipid, glyceroglycolipid or sphingoglylcolipid.

Claims 1-6, 10, 12-17, 19-20 and 23 are rejected as anticipated by Burke (U.S. Patent No. 5,552,156). Burke is also cited as showing multilamellar vesicles containing camptothecins. The lipids include DSPC and cholesterol. Although Burke does not teach the size of the vesicles, the Examiner contends since the preparations are only vortexed and not sonicated, they must be larger than 120 nm.

First, Burke's liposomes contain cholesterol and so, Burke does not teach a liposome prepared of lipids consisting of phospholipid, glyceroglycolipid or sphingoglylcolipid.

Second, regarding the Examiner's contention concerning vortex processing, Applicants submit the additional experimental data attached at Tab A. As illustrated, the average particle size of liposomes prepared, like Burke, by being vortexed without sonication is >500 nm (see Comparative Example 5). Accordingly, Burke does not teach this feature of the present invention either.

Claims 1-6, 9-10, 12-17, 19-20 and 22-23 are rejected under 35 U.S.C.§102 (a) or (b) as anticipated by EP 0 850 646. In support of this rejection, the Examiner argues EP '646 discloses liposome formulations, containing indolocarbazole derivatives, made from hydrogenated phospholipids, PEG-DSPE and cholesterol.

It is noted EP '646 does not explicitly teach multilamellar liposomes, or the size of any liposomes but, as with Burke, the Examiner contends formation of

multilamellar vesicles larger than 120 nm is said to be implicit since the lipid film was hydrated and vortexed rather than sonicated. However, again with reference to the comparative sheets at Tab A, EP '646 too fails at least to teach a liposome having the average particle size noted in the pending claims.

Claims 7, 9-11 and 21-25 are also rejected under 35 U.S.C.§103 (a) as obvious over Law. The Examiner states that it would have been obvious to one of ordinary skill in the art to regulate extrusion to prepare liposomes of any sizes.

Disregarding, *ab initio*, that this is not motivation for making such change required by the Federal Circuit, it is further seen that the present invention provides unexpectedly superior results. Thus, even assuming, *arguendo*, that a *prima facie* case of obviousness is presented, such is overcome on the present record.

As the Examiner is aware, the present invention broadly relates to a liposome preparation of encapsulated drugs having an average particle size of the liposomes are 120 to 500 nm wherein the lipids have a phase transition temperature higher than *in vivo* temperature and are selected from the group consisting of phospholipid, glyceroglycolipid and sphingoglylcolipid.

Concerning average particle size, liposomes having a large average particle size are highly distributed in tissue and provide low plasma concentration of the encapsulated drug (see Chem. Pharm. Bull., 41(3), 599-604 (1993) at Fig. 3). In order to avoid such effects, liposomes having a very small average particle size (< 120 nm) are consistently preferred in the art (for example, see Cancer Chemother. Pharmacol. , 47, 15-21 (2001)).

On the other hand, liposomes having a small (< 120 nm) average particle size exhibit unacceptable drug leakage as shown in Test Example 1 of the present application (see comparative Example 1). In contrast, the liposomes of the present invention (having an average particle size of 120 - 500 nm) unexpectedly inhibit drug leakage.

Claims 8-9, 11, 18, 22 and 24 are rejected under 35 U.S.C. § 103 (a) as being obvious over Woodle. In support of the rejection, the Examiner states it would have been obvious that any desired drug could be encapsulated within Woodle's liposomes. Initially, Applicants respectfully wish to point out, as discussed above, that Woodle does not teach a liposome of phospholipid, glyceroglycolipid and sphingoglylcolipid.

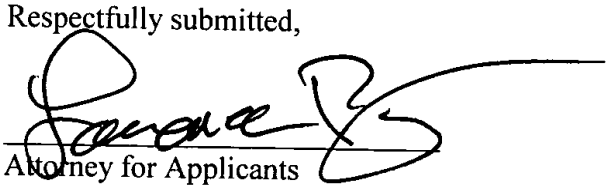
Nonetheless, Applicants submit the additional experimental data at Tab A. As shown in Comparative Example 4, Woodle's liposomes containing cholesterol fail entirely to inhibit leakage of encapsulated drug in the presence of biological components (see Test Example 2). On the other hand, liposomes according to the present invention do inhibit the leakage of encapsulated drug in the presence of biological components (see Test Example 1)

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 3-5, 8-12, 16, 19-20 and 22-39 remain presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,



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